REMARKS

Applicants' undersigned Attorney would like to thank Examiner Rollins for the helpfulness and courtesy she extended during a recent telephone interview, at which time this Amendment was discussed. Although no agreement was reached during this interview, the Applicants believe that the foregoing Amendment to the specification, along with the arguments presented herein, are consistent with the discussions made during the interview and are sufficient to overcome the Examiner's rejection of the pending claims.

The Applicants have attached hereto, as requested by the Examiner, copies of prior art publications specifically directed to warts and the treatment of warts. As is evident from these documents, the position enunciated by the Applicants regarding the distinguishing characteristics of the present invention over the prior art is clearly and unequivocally supported, with the unique aspects of the present invention becoming immediately apparent. For these reasons, the Applicants believe that all of the pending claims are in condition for allowance.

In the claims presently pending before the Examiner, Claims 1, 28, 29, 31, 33, 35, and 37 are all independent Claims directed to the treatment system of the present invention. In each of these claims, the treatment system is defined as comprising a holding and supporting member constructed for being securely retained on the desired

site and being formed substantially entirely from foam plastic material, a delivery patch or exothermic pad positioned on the desired site, in cooperating relationship with the holding and supporting member. In addition, the system incorporates and at least one systemic medication applied to the desired site, which systemic medication exhibits improved or enhanced penetration from the application of a heat gradient and, further, comprises one selected from a specifically defined group of systemic medications. In each of these independent claims, different specific medication groups are defined and precisely detailed.

In rejecting the present claims, the Examiner has asserted that (1) the prior art Dvoretzky patent discloses the use of keratolytic agents in combination with heat therapy, and (2) keratolytic agents have been established by the Applicant as systemic medications. As a result of these two assertions, the Examiner has concluded that the detailed, specific systemic medications, defined in each of the independent claims, is merely a substitute for the keratolytic agents and would be obvious to someone having ordinary skill in this art. This position is inaccurate and untenable.

By reviewing the enclosed documents, which represent pertinent sections from the major textbooks in Dermatology, it is immediately apparent that keratolytic agents, such as salicylic acid, are <u>not</u> systemic medications, as asserted by the Examiner. Clearly, keratolytic agents in general, and salicylic acid in particular, are described in each of these textbooks as topical medications applied to the skin surface for physically

acting upon the thickened area of the wart, with the hope of reducing the thickness of this area.

A review of this documentation clearly and unequivocally reveals no teaching or suggestion that keratolytic agents and/or salicylic acid are systemic medications which function by entering the bloodstream for obtaining a desired beneficial result by deep subcutaneous penetration. Furthermore, the enclosed documentation also confirms absolutely no prior art of teaching which would lead one having ordinary skill in this art to conclude that keratolytic agents and/or salicylic acid exhibit improved or enhanced penetration into the body of an individual by applying a heat gradient thereto.

The enclosed references unequivocally define the action of keratolytic agents as being topical in nature, affecting only the skin surface by breaking down some of the cells. Then, by employing abrasive, such as files and pumice stones, these cells can be removed.

In view of this clear teaching, the Applicant has amended the specification of this pending patent application by deleting the reference to keratolytic agents in Markush groups which contain systemic medication. Since the inclusion of keratolytic agents in this group is erroneous, correction has bee made in this Amendment.

In each of the independent claims presently before the Examiner, specific limitations are found regarding the incorporation of at least one medication which is applied to a desired site with that medication being selected from a specifically defined

group of systemic medications which exhibit improved or enhanced penetration from the application of a heat gradient. Clearly, no comparable teaching is found in the prior art, as asserted by the Examiner. Consequently, the Applicants maintain that each of these independent claims is clearly in condition for allowance.

Furthermore, the Applicants maintain that the specifically defined systemic medications detailed in the independent claims, both by categories such as corticosteroids, chemotherapeutic agents, antihistamines, anti-parasitics, antioxidants, immunommodulators, and anti-neoplastics (as detailed in claim 1), as well as the specific systemic medications falling within each of these categories (as detailed in each of the remaining independent claims), are incapable of being dismissed as obvious. Clearly, the enclosed documentation unequivocally describes keratolytic agents and salicylic acid as topical agents primarily used for warts. There is no doubt that this teaching is incapable of being employed in realistically establishing a supportable rejection that the systemic medications defined in the pending claims of the present application represent merely obvious variations of keratolytic agents or salicylic acid.

In view of the foregoing, the Applicants believe that the patentability of all of the pending claims over the cited references has been clearly established and the issuance of a notice of allowability is earnestly solicited. If any questions remain which may be resolved by a telephone interview, Applicants' undersigned Attorney would gladly

discuss such issues with the Examiner at the Examiner's convenience. For this purpose, Applicants' undersigned Attorney has provided his telephone number below.

Respectfully submitted,

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Arch. Derm. Res. 257, 293–297 (1977)

Archives for
Dermatological
Research

"Keratolytic" Effect of Salicylic Acid

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Summary. The "keratolytic" effect of salicylic acid was examined in guinea-pig skin. Using a fluorescent staining method the str. corneum cells could be seen to rapidly become detached. The cellular walls remained unchanged. This drug therefore appears to primarily reduce the intercellular cohesiveness of the horny cells.

Zusammenfassung. Der sogenannte keratolytische Effekt von Salicylsäure an der Hornschicht wurde unter Verwendung der FITC-Darstellungsmethode untersucht. Es zeigte sich, daß die Hornzellen ohne Verlust der Membranfluorescenz abgelöst werden. Die Zellen bleiben intakt. Salicylsäure wirkt somit im Bereiche der intercellulären Verkittung. Neben der „Keratolyse" zeichnet sich Salicylsäure durch fehlende Epidermotoxicität aus.

Since decades salicylic acid serves as the principal keratolytic agent in dermatologic practice. Despite its wide use and high clinical effectiveness the mode of action of this drug is rather unknown. One of the reasons for this lack in knowledge has been the inability to visualize morphologic details of the horny layer. Routine histologic processing of skin specimens usually destroys the horny layer–thus only limited information about the structure of this tissue can be gained.

In order to obtain more information on drug-induced changes of the horny layer we used the FITC-staining method [1]. As shown earlier, this technique is based upon the high affinity of fluorescent isothiocyanates to sulfur-rich epidermal proteins [3]. Such proteins are constructing the cellular wall in corneocytes [5] thus by this staining reaction the stratum corneum can be clearly visualized.

With this method we studied the effect of salicylic acid (SA) on the horny layer.

Materials and Methods

The ears and soles of feet of adult guinea-pigs (300–450 g weight) were used. The animals were kept under normal housing conditions and received drinking water and food (Altromin®) ad libitum.

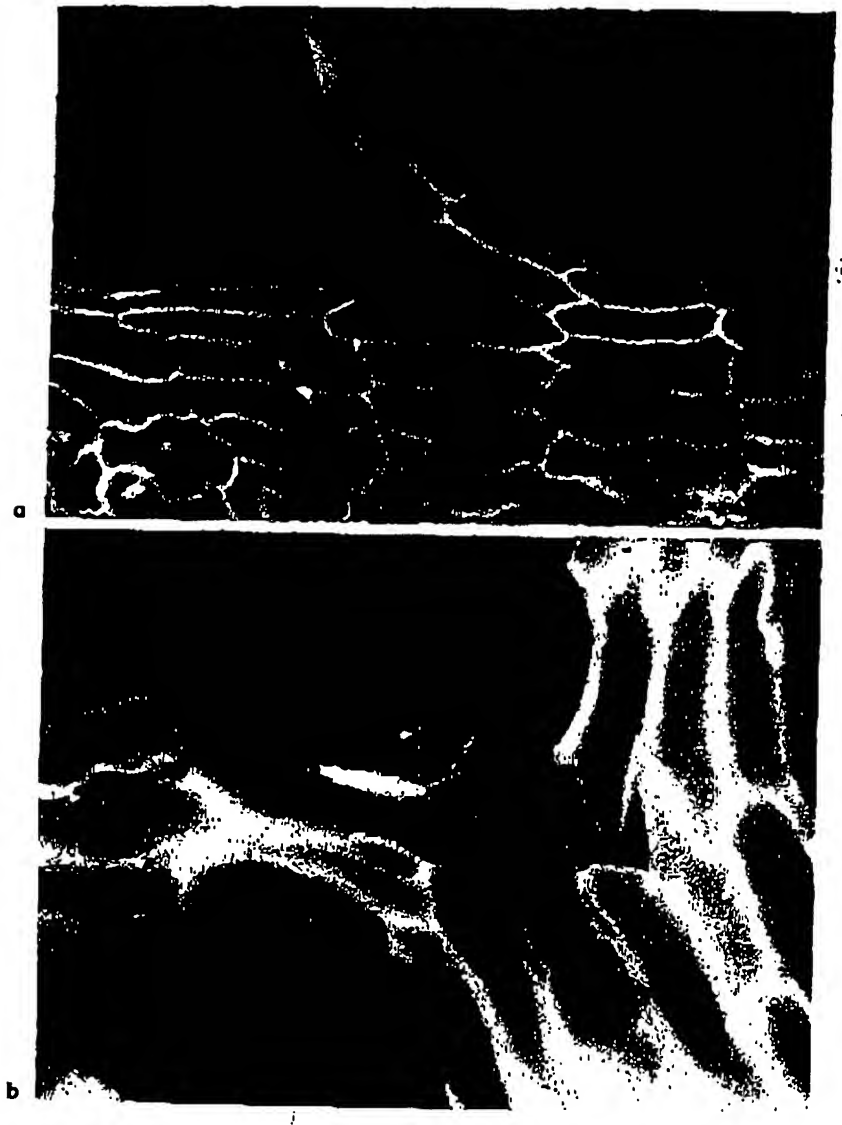
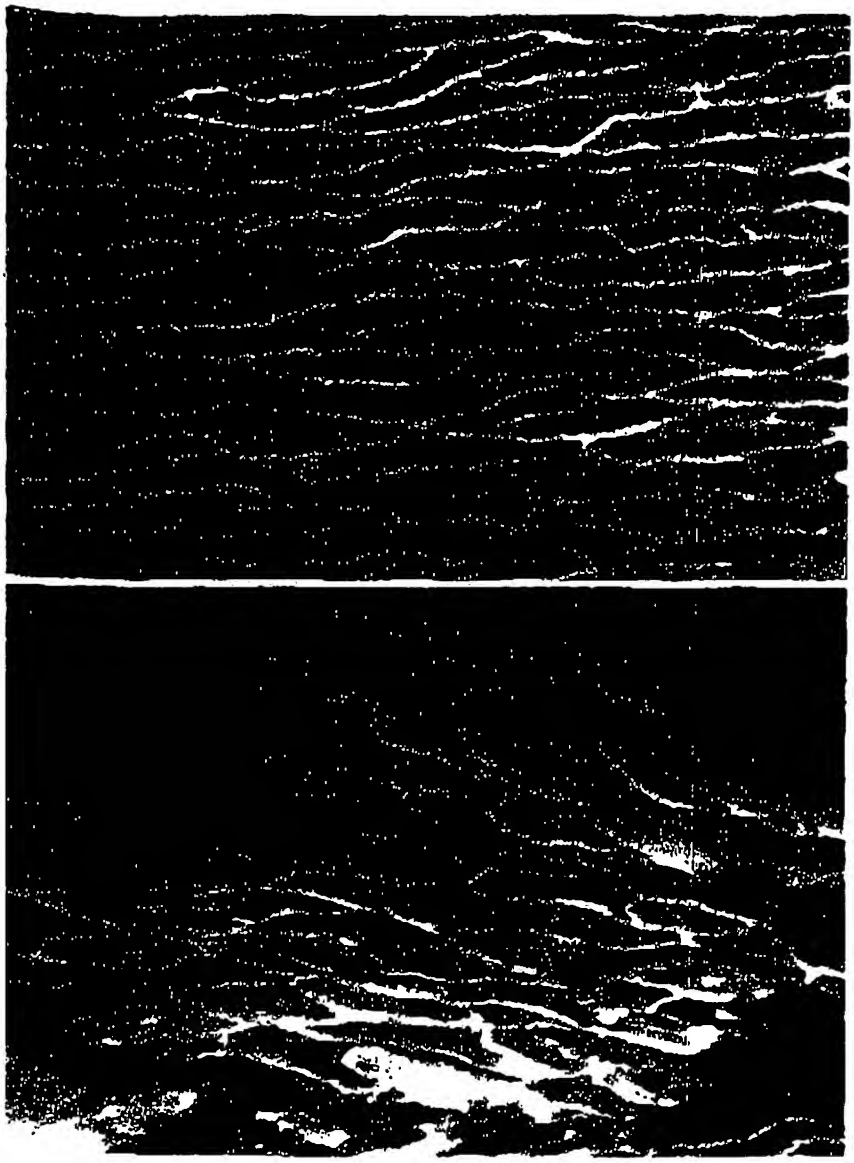


Fig. 1a and b. Salicylic acid induced-desquamation in guinea pig ear str. corneum. Intact corneocytes become detached not losing the staining of the cellular walls. a Desquamation in stacked str. corneum (Magnif. × 280). b Separation of single cells (Magnif. × 700)

A saturated (50%) solution of salicylic acid in ether was pipetted on the ears and soles after sacrificing the animals by neck-dislocation. The tissue specimens were incubated in humidity chambers at 25°C after the ether had evaporated.

After 10 h the specimens where rinsed shortly in ether and cryostat sections (4 µm thickness) were prepared. For the process of cutting special care was taken to move the edge of the sectioning



ig. 2a and b. Str. corneum of guinea pig foot pat. a After ether-treatment no structural changes are ten. (Magnif. × 280). b Treatment with SA (50%) causes loss of intercellular stickiness. Magnif. × 280)

nife from the stratum corneum down towards the dermis. By this procedure loss of horny cells was revented. The sections were stained as previously described using FITC (Serva) diluted to 1:10000 id mounted under 1% acetic acid [1]. The specimens were observed under a fluorescent microscope Zeiss, filter combination BG 3, 41/50). photographs were taken using Agfapan 400 or Ilford FP 4.

Fig. 3. Guinea pig-sole after stretching. No salicylic acid applied. The upper cells are ruptured while remaining in tight contact with neighbouring cells. (Magnif. × 280)

Results

Gross inspection of the slides revealed no difference between the treated and untreated horny layers. In both groups the cellular outlines showed brilliant fluorescence while the corneal cytoplasm remained essentially unstained. It was noted however that in SA-treated stratum corneum fluorescent ring-like structures were present resembling the shape of the otherwise undetectable nucleus (Fig. 1a, 2b).

When mechanical stress was applied to the specimens by slight movement of the cover slips the SA-treated str. corneum broke up into pieces. Groups of cells became separated, sometimes the entire horny layer down to the keratogenous zone desintigrated into single cells. In all cases the cellular outlines remained intact (Fig. 1a and b).

Under the same stress the control specimens became elongated and the cells showed considerable flattening. Opposite to the treated str. corneum however no cellular separation occured. When the untreated stratum corneum was maximally stretched the cells ruptured in such a way that two separate portions of one cell remained firmly attached to neighbouring cells (Fig. 3). No intercellular separation was detected in the control group, while in the SA-treated stratum corneum this was constantly present.

Discussion

The present results show that the "keratolytic" effect of SA consists in a reduction of intercellular stickiness. Apparently the socalled cementing substances are the site of action, not however the stratum corneum cell itself.

The biochemical nature of the intercellular material is rather unknown [5]. It is of interest however that the intercellular cohesion appears to be stronger than the horny cell itself–breakage lines are observed passing through the cells.

Salicylic acid is a drug the benefical effects of which have been found by empirical means. Our preliminary experiments with other simple acids revealed very similar effects in the str. corneum as compared to SA. However with acetic acid and sulfuric acid for instance severe damage of the living epidermis was seen. This is in contrast to SA, which has been shown to cause no epidermal change beneath the str. corneum [4]. Besides desquamation the therapeutical uniqueness of SA appears to be based upon the lack of epidermotoxicity.

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Received October 14, 1976

Text Book

Mucocutaneous Manifestations of
VIRAL DISEASES

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MARCEL DEKKER, INC.

NEW YORK • BASEL

ISBN: 0-8247-0450-9

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
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World Wide Web
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Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

location of the HPV genome within the tissue. When exon-specific probes are used, this test also allows localization of the expression of specific viral genes. The drawback of these tests is that all of these hybridization methods are relatively labor intensive, and with Southern and dot blotting, require more tissue than may be readily available.

The most sensitive and currently preferred method for detection of HPV in the research laboratory makes use of the polymerase chain reaction (PCR), a technique that allows primer-directed amplification of very small amounts of viral DNA [144–147]. With the most commonly employed PCR methods, the DNA primers are designed in such a way that they will hybridize with and amplify sequences in the L1 gene from a large number of HPV types (termed *degenerate primers*). The amplified product can then be more stringently hybridized with HPV type–specific probes to allow HPV typing. This method is both sensitive and specific. Using PCR methods, it is possible to detect as few as 10 to 100 copies of the viral genome with very small amounts of tissue, whereas the traditional blotting methods require 10^5 to 10^6 copies. The increased sensitivity of these methods has been of particular use in epidemiological studies to allow more accurate estimates of HPV incidence.

Whereas these methods are still mostly used in research laboratories, they are becoming commercially available and have been used in certain clinical settings. Clinical use of HPV typing has most commonly been used in conjunction with Pap smear for the detection of HPV infection. It has been shown that the histological criteria for HPV infection, such as koilocytosis and dyskeratosis, underestimate the incidence of infection and typing adds to the sensitivity of this screening. A method for detection of HPV DNA with sensitivity and specificity similar to that of PCR is the hybrid capture assay. An improved version of this assay, hybrid capture II, is generally acceptable for clinical use. Knowledge of the specific HPV type gives information on the risk for development of cervical cancer and can help in planning the frequency of follow-up for patients. At the present time, HPV typing is not routinely done, but has been implemented in cases with equivocal histological results. HPV typing has been used infrequently for the detection of high-risk HPV-5 in patients with EV. In the evaluation of children with condyloma acuminata, epidemiologists have used HPV typing to evaluate the likelihood of child abuse. These studies have shown that the incidence of child abuse in these cases may actually be lower than had previously been suspected [15].

TREATMENT

Unfortunately, there are no specific antiviral treatments for HPV infection (Table 12–5). Some warts prove very difficult to eradicate, and recurrences are very common. Most current treatment regimens for warts involve physical destruction of the infected tissue. Decisions regarding treatment must take into account the type and location of warts, the age of the patient, and the immunological status of the patient. Because evidence indicates that in healthy children, two thirds of warts will spontaneously remit within 2 years [148], not every wart needs to be treated. If the warts are not physically or psychologically bothersome, a decision to postpone treatment may be made, particularly in younger children, because most of the treatment modalities involve some discomfort. The situation is somewhat different with genital warts because of their sexually transmitted nature and the risk of malignancy. In patients with anogenital warts, the sexual partners should be examined and treated, and women should have colposcopic examination of the uterine cervix and Pap smear. If there are anal warts, anoscopy should be considered. Patients need to be counseled as to the risks of transmission of the warts. An important consideration, particularly in the treatment of genital warts, is that the treatments currently available do not eliminate subclinical or latent infection [149]. HPV DNA has been detected in the clinically normal skin adjacent to treated genital warts, and the presence of HPV correlates with higher rates of wart recurrence [20]. Thus, patients need to be counseled as to the likelihood of recurrence. Long-term follow-up is recommended for patients with cervical or vaginal lesions. Although the lesions of Bowenoid papulosis will sometimes spontaneously remit, they represent a potential reservoir of HPV 16 and should be treated.

Topical Therapies

Topical acidic preparations are a commonly used first-line therapy for warts. Most commercial preparations use varying concentrations of salicylic acid in a number of different vehicles. The salicylic acid causes keratolysis of the infected tissue, and the success rate of this method is good with prolonged therapy. When hand warts, simple plantar warts, and mosaic warts are treated for 3 months, resolution has been seen in 45 to 84% [150]. The main drawback is that this method is time consuming and requires a high degree of patient motivation over a prolonged period of time. The application of caustic acids, such as 50% trichloroacetic acid, can be used for the destruction of warts in the office setting. These acids cause destruction of cellular proteins and induce inflammation and cell death. Another topical agent is cantharidin, which is a caustic extract from the green blister beetle that causes vesiculation and acantholysis of the skin. The major side effect of this treatment is that it can induce pronounced inflammation and discom-

Table 12–5. Treatment of Warts

Treatment	Method
Common warts	
Salicylic acid	Available over the counter, and can be applied at home, once or twice daily, for several months. The wart is soaked in warm water to soften the tissue, followed by removal of the keratotic skin with an emory board or pumice stone. Salicylic acid is then applied to the wart. An adhesive bandage may be applied to enhance penetration. Patches or pads impregnated with salicylic acid are also available.
50% Tricholoacetic acid	Wart is pared down, then acid is applied in the office, either alone or under occlusion. The area should be rinsed off about 2 hr later. Therapy can be repeated at weekly intervals until resolution of the wart.
Cantharidin	This is applied to wart surface with or without occlusion, and left in place for 8–24 hr, after which a blister has usually formed. Therapy may be repeated after healing of the blister, at 1–3 wk intervals.
Cryotherapy with liquid nitrogen	The keratotic material of the wart can be pared off, followed by freezing with liquid nitrogen, usually with two freeze-thaw cycles. The amount of time required for freezing varies with the thickness of the wart. Therapy often has to be repeated to clear the wart completely, usually at 2–3 wk intervals.
Electrodessication	Sometimes used for recalcitrant warts. The area must first be anesthetized, followed by electrodessication of the wart until a white crust appears. This crust is then curretted. Repeated treatments are usually required.
CO_2 laser	Expensive and typically reserved for recalcitrant warts
Bleomycin	Intralesional bleomycin can be used for the treatment of recalcitrant periungual and plantar warts. 0.5–1.0 U/ml concentration is injected directly into the wart tissue
Surgical excision	Reserved for debulking large exophytic warts resistant to therapy
Flat warts	
Retinoic acid 0.05%	Applied daily to warts until desquamation occurs, which is sometimes accompanied by mild local irritation
Condylomata	
Podophyllin	Used primarily in the treatment of genital warts, because it is more effective on mucosal surfaces. (contains mutagens) (not standardized)
Podophyllotoxin 0.5% solution or gel	Applied once or twice daily, stopping if marked irritation occurs (patient applied) (high recurrence rates)
5-Fluorouracil (5%) solution	Primarily used for verruca plana and condyloma; (highly inflammatory) (teratogenic)
Interferon-alpha	Given by injection; flu-like side effects
Cidofovir	Not available in a topical preparation, but can be compounded as a cream or gel (e.g. 1–3%)
Imiquimod 5% cream	Applied (by patient) three times weekly overnight (low recurrence rates)

fort. Both trichloroacetic acid and cantharidin can cause marked epidermal destruction and potential scarring; thus, they are used only in the office setting.

Topical chemotherapeutic agents have also been employed in the treatment of warts. Podophyllin is a complex plant resin that is a potent antimitotic agent. This compound is contraindicated during pregnancy. Podophyllin is not a standardized preparation, and the concentration of its active ingredient, podophyllotoxin, can vary significantly. In addition, podophyllin contains two mutagens that have been epidemiologically implicated as being carcinogens. Purified solutions of podophyllotoxin are now available that have improved the safety profile and have been approved for treatment of genital warts. Podophyllotoxin 0.5% solution or gel is useful for the treatment of warts, but the local reaction can involve an erythema, burning, and superficial erosions. Because podophyllotoxin has no antiviral or immunodulatory activity, recurrences of anogenital warts are common. The antimetabolite 5-fluorouracil (5-FU) in a 5% solution has been used for the treatment of warts, primarily verruca plana and condyloma. Here again, this agent can induce inflammation, erosions, and postinflammatory hyperpigmentation and is teratogenic. 5-FU has also been used in combination with other destructive modalities to decrease the frequency of recurrences [151]. Intralesional therapy with the antimetabolite, bleomycin, is thought to act by inhibiting both cellular and viral DNA synthesis, but may also act by enhancing the host's immune response to the virus. Reported side effects include Raynaud's phenomena with periungual warts and extensive tissue necrosis, and thus this agent must be used cautiously.

A newer topical agent for the treatment of warts is imiquimod, an imidazoquinolin heterocyclic amine. This drug has been approved for topical treatment of anogenital condyloma. In a 5% cream formulation, imiquimod is applied by the patient overnight three times weekly. Although imiquimod has no specific antiviral effects, it is immunomodulatory and is thought to exert its effect against papillomavirus through induction of cytokines including interferon-alpha and TNF-α [152,153]. Clinical studies have shown clearance of genital warts in approximately 50% of patients (Fig. 12–63). There are no systemic adverse effects, and local irritation is the most common side effect [154]. Recurrences following complete clearance of condyloma acuminatum have been very low (e.g., 13% during a 3-month follow-up period in one study) [154]. Current studies have demonstrated the efficacy of imiquimod (often as adjunctive therapy) against nongenital warts.

Flat warts can be very resistant to therapy, but often respond well to the application of retinoic acid 0.05%. It probably works by acting as a keratolytic agent. Immunotherapy has also been employed in the treatment of warts. Induction of an allergic reaction in the area of a wart may result in clearing. Dinitrochlorobenzene (DNCB) has traditionally been used for this, but concerns over its mutagenicity make its use controversial.

Destructive Procedures

Cryotherapy with liquid nitrogen is a commonly used treatment for warts on any part of the body. It works by destruction of the frozen tissue and induction of an immune response in the area. There is pain during treatment, and patients may note throbbing in the hours after the procedure. After several hours up to a few days, a clear or hemorrhagic blister develops that generally heals in 1 to 2 weeks. Occasionally, healing results in a clear area surrounded by a ring of new warts that produces a "halo" or "doughnut" effect (Fig. 12–64). Electrodessication has been used in the treatment of warts resistant to cryotherapy. This procedure is commonly associated with scarring after healing and thus should be avoided on plantar surfaces. The use of surgical excision of warts is usually reserved for debulking a large exophytic wart resistant to therapy and, because of high recurrence rates, must be used in conjunction with other treatment modalities. Mohs' micrographic surgery has been successfully used in the treatment of verrucous carcinoma. Treatment of verrucous carcinoma with ionizing radiation is strictly contraindicated because it is associated with recurrence of tumors with a greater invasive potential. The CO_2 laser has been used to treat warts, particularly those in which precise control of the extent of destruction of tissue is required and those refractory to other therapies. This is an expensive method of treatment, and reports of the success are highly variable. Infectious HPV particles have been identified in the vapor plume with laser therapy, and adequate protection with goggles and surgical mask is important [155].

Interferon

The interferons are a large family of proteins that are thought to have antiproliferative, antiviral, and immunomodulatory effects. Intralesional and parenteral interferon has been evaluated in the treatment of refractory genital warts. Intralesional therapy with interferon-α has led to clearing of warts in 36% of patients [156–158], but topical therapy with leukocyte interferon has not been shown to be effective [159]. Parenteral therapy with interferon-α or interferon-β led to clearing of genital warts in the majority of patients [160–162]. Intralesional therapy with interferon has also been investigated in the management of difficult cases of laryngeal and respiratory papillomatosis and EV.

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FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE

Sixth Edition

1234567890 KGPKGP 09876543

Set: ISBN 0-07-138076-0
Volume I: ISBN 0-07-138066-3
Volume II: ISBN 0-07-138067-1

This book was set in Times Roman by TechBooks, Inc. The editors were Darlene Cooke, Susan R. Noujaim, Lisa Silverman, and Peter J. Boyle; the production supervisor was Richard Ruzycka; the cover designer was Elizabeth Pisacreta; Barbara Littlewood prepared the index. Quebecor World Kingsport.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data
Fitzpatrick's dermatology in general medicine.—6th ed. /
Irwin M. Freedberg . . . [et al.]
p. ; cm.
Includes bibliographical references and index.
ISBN 0-07-138076-0
1. Dermatology. 2. Skin–Diseases. 3. Cutaneous manifestations of general diseases. I. Fitzpatrick, Thomas B. (Thomas Bernard), 1919–
II. Freedberg, Irwin M.
[DNLM: 1. Skin Diseases. 2. Skin Manifestations. WR 140 F5593 2003]
RL71.D46 2003
616.5—dc21 2002021932

Tazarotene

Tazarotene is useful in treatment of mild to moderate plaque psoriasis. Tazarotene normalizes abnormal keratinocyte differentiation, has anti-hyperproliferative activity, and is anti-inflammatory.[45] It is nonsensitizing, nonphototoxic, and nonphotoallergenic. Tazarotene is available in a 0.05% and 0.1% gel. It is effective as a once-daily application, and clearing can occur in 12 weeks. The most common side effect is local skin irritation.

WART THERAPIES

Dinitrochlorobenzene (DNCB)

DNCB is a potent sensitizer. The mechanism of action of topical DNCB may be to systemically stimulate T_H1 cell responses.[46] DNCB is mutagenic and potentially carcinogenic.

Diphenylcyclopropenone

Diphenylcyclopropenone is also used in contact immunotherapy in much the same way as DNCB. However, it is not mutagenic.

5-Fluorouracil

5-Fluorouracil is a pyrimidine analogue that inhibits thymidine synthetase, thereby inhibiting DNA synthesis. In addition to its use in actinic keratosis, it has been used successfully in the treatment of flat, mosaic, and genital warts. Its effectiveness may be heightened by an occlusive dressing or in combination with salicylic acid.

Formaldehyde

Formaldehyde acts similarly to glutaraldehyde. It is useful in the treatment of mosaic plantar warts, which are especially resistant to therapy. A 3% solution is used to soak the infected area for 15 to 20 min daily. The solution can be reused.

Glutaraldehyde

Glutaraldehyde is viricidal. It hardens the wart surface, thereby facilitating paring. It stains skin brown, making it less cosmetically appealing. The benefit to using this agent is that it reduces viral shedding from the wart surface, thus reducing the infectious risk.

Imiquimod

Imiquimod belongs to a class of imidazoquinolinamines that has antitumor and antiviral activity. The mechanism of action is uncertain. It exerts no direct antiviral effect within the mammalian cell in vitro, but does activate the immune system via cytokine induction.[47] Imiquimod is available in a 5% cream (see also Chap. 250).

Mono-, Di-, Trichloroacetic Acids

Eighty percent monochloroacetic acid penetrates the skin and may produce necrosis of the epidermis by blister formation. Saturated dichloroacetic acid or trichloroacetic acid in concentrations of 50% to 80% are less powerful but still effective in the management of warts.[48] Occlusive dressings enhance effectiveness. The application needs to be repeated at 1- to 2-week intervals until complete resolution.

Podophyllin Resin

Podophyllin is an extract from the dried roots of either *Podophyllum peltatum* or *P. emodi*. It acts as an antimitotic agent by preventing the formation of mitotic spindles. It is available in a range of concentrations in various vehicles, such as tincture of benzoin, alcohol, or flexible collodion, and is used as a treatment for genital warts.

Podofilox

Podofilox is the active ingredient obtained upon purification of the podophyllin resin. It does not contain any of the ingredients responsible for the toxicity of podophyllin.

Salicylic Acid

The use of salicylic acid in treating warts lies in the destruction of the epidermis in which the virus is present. Salicylic acid is more irritating than some other over-the-counter preparations.

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Warts

Diagnosis and Management
An Evidence-based Approach

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Taylor & Francis Group
LONDON AND NEW YORK

First published in the United Kingdom in 2003
by Martin Dunitz, Taylor & Francis Group plc, 11 New Fetter Lane, London EC4P 4EE

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A CIP record for this book is available from the British Library.

ISBN 1 84184 240 0

Distributed in the USA by
Fulfilment Center
Taylor & Francis
10650 Tobben Drive
Independence, KY 41051, USA
Toll free tel: +1 800 634 7064
E-mail: taylorandfrancis@thomsonlearning.com

Distributed in Canada by
Taylor & Francis
74 Rolark Drive
Scarborough, Ontario M1R 4G2, Canada
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Distributed in the rest of the world by
Thomson Publishing Services
Cheriton House
North Way
Andover, Hampshire SP10 5BE, UK
Tel: +44 (0) 1264 332424
E-mail: salesorder.tandf@thomsonpublishingservices.co.uk

Composition by Scribe Design, Gillingham, Kent, UK
Printed and bound in Spain by Grafos S.A. Arte Sobre Papel

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5 Acids in the treatment of viral warts

Angeline F Lim, Sanjay Sheth and Robert T Brodell

Historical aspects • Classification • Basic science • Clinical studies • Favored treatment methodology • Adverse effects • Cost–benefit considerations • Case reports • References

As most people will have been afflicted with at least one wart at some point during their lives, and there is little urgency for immediate clearing, it is no surprise that there is an entire industry catering to the public demand for home wart treatments.

Americans spend more than $US45 million annually on over-the-counter wart products.[1] Despite the broad array of formulations available, most home treatments rely on an acid as their active ingredient, most commonly salicylic acid. For some over-the-counter treatments, salicylic acid is combined with lactic acid. There are other caustic agents available to the physician for treatment in the surgery, including monochloroacetic acid (MCAA), dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA). In this chapter, we review the treatment of warts with various types of acids, emphasizing primarily home treatments.

HISTORICAL ASPECTS

Salicylic acid and its derivatives have been used for centuries in the treatment of many common ailments. The Egyptians were the first to use salicylic acid and this was continued through the Greek civilization, where Hippocrates documented the use of a substance found in willow bark for the treatment of headaches and fevers. In America, Native American medicine men used willow bark in a similar manner. In 1838, Johan Andreas Buchner became the first person to isolate salicylic acid as the active compound in willow bark.[2] In response to its unpleasant side effects, a German chemist named Felix Hoffmann modified salicylic acid into acetylsalicylic acid or aspirin in the 1890s. In 1923, prescriptions for a salicylic acid and lactic acid combination, similar to the formulations available for home treatment today, were first used in the treatment of warts.[3]

CLASSIFICATION

Acids used in the home treatment of warts are available in a variety of strengths and bases. The most commonly used product is salicylic acid, available in variable strengths in the form of creams, gels, lotions, ointments, plasters and topical solutions, e.g. most over-the-counter solutions have concentrations of 17% salicylic acid (Occlusal-HP) whereas plasters can have as much as 40% (Clear Away). It may also be formulated with other additives such as lactic acid (Duofilm). The scientific literature has reported the use of salicylic acid in

strengths up to 70% in clinical studies, which may be compounded by many pharmacists.[4] MCAA, DCAA and TCAA are generally used as a physician-applied treatment for use in the surgery.

BASIC SCIENCE

There is general agreement about the mechanism for salicylic acid in the treatment for warts. It is a keratolytic agent, which disrupts intercellular cohesiveness, causing desquamation of the human papillomavirus (HPV)-infected epidermal cells.[5] It may also cause triggering of a beneficial immune response, leading to regression.[6]

Other types of acids, including TCAA, work in a similar manner and because of their potency can be considered a form of chemical cautery.[7] TCAA non-specifically hydrolyses cellular proteins, leading to inflammation and cell death of both virally infected and normal cells.[8] In addition, it also provokes a humoral immune response that complements and strengthens the mechanochemical effects.[9]

CLINICAL STUDIES

In 2001 Sterling et al[6] set forth guidelines for the management of cutaneous warts. They considered salicylic acid to be first-line therapy for small warts. Available over the counter for home therapy, it is certainly convenient, although there have been relatively few placebo-controlled trials for accurate determination of its efficacy in the treatment of warts. Response rates for this modality are highly variable, ranging from 40% to 84%, with an average of 61%.[10] One of the earliest studies, conducted by Bunney in 1973,[11] found no difference in efficacy between daily application of 5% 5-fluorouracil in dimethyl sulphoxide and a paint containing 16.7% salicylic acid and 16.7% lactic acid in four parts of flexible collodion (Duofilm) in the treatment of plantar warts (47–53% clearing). Later in the two-centre Edinburgh and Dundee trial, no statistical difference was found between the cure rate for hand warts treated with liquid nitrogen (69%) and those treated with equal parts of salicylic acid and lactic acid in four parts of flexible collodion (69%).[3] In another study, a combination of 12% salicylic acid, a small amount of lactic acid and a collodion gel (Salactac) applied nightly cured or markedly improved common warts in 75% of patients.[12] In warts treated with 15% salicylic acid in a karaya gum patch (TRANS-VER-SAL system), a 69% cure rate was found for verruca vulgaris.[13] This treatment also proved to be very safe and convenient.

A 60% cure rate was reported after 6 weeks of treatment with 21% salicylic acid polymeric matrix delivery system (Transplantar).[14] Topical salicylic acid solutions, such as the high-potency (26%) salicylic acid in a novel polyacrylic vehicle (Occlusal-HP), have an improvement or cure rate of 81% after only 2 weeks of treatment.[15] Unfortunately, those topicals with more than 17% salicylic acid have been removed from the US market pending further study of safety and efficacy. Most recently, van Brederode and Engel[4] reported an 89.2% resolution rate using a novel combination of weekly cryotherapy with Verrucafreeze and daily topical 70% salicylic acid with a mean treatment time of 7.6 weeks and an average of just 4.05 applications of Verrucafreeze.[4]

Treatment with salicylic acid is classified as level 1 based on the strength of evidence using our modified Evidence-based Medicine System (see Chapter 19). Its use is supported by good evidence from well-designed randomized controlled trials with narrow confidence intervals.[3,4,10–15] Larger randomized placebo controlled studies would be helpful to fully elevate this treatment method.

There is also significant variation in the clinical success rates for the other types of acid used in treating warts. Once-weekly treatments with 95% TCAA showed 70–81% response rates with similar efficacy; when compared with cryotherapy. In these studies, both TCAA and cryotherapy also showed similar adverse effects in the treatment of genital warts.[17–19] Higher success rates (90%) for MCAA were reported by Dagnall[20] but have not been replicated by others. A 66% cure rate using various formulations of MCAA was achieved by both Dutta[21] and Steele and Irwin[9] in separate trials. Treatment with MCAA, DCAA and TCAA is classified as level IIa based on our Modified Evidence-based Medicine System (see Chapter 19).

FAVORED TREATMENT METHODOLOGY (Table 5.1)

Salicylic acid is an excellent first-line home treatment for plane warts on the face, as well as for small warts on the hands and feet.[6] Many clinicians prefer to use collodion gels because of their ease of application and acceptability by patients. They can be applied quickly and accurately to the wart while drying quickly to form a transparent film.[8,22,23]

The protocol used by the authors is as follows: first, any film from previous treatments should be peeled off, and the wart mechanically débrided of any excess keratotic material. This may be achieved by using sandpaper, an emery board, pumis stone or nail file. This is done to ensure that the medication will destroy deeper layers of the wart. In addition, salicylic acid is combined with cantharidin, liquid nitrogen and other methods available in the surgery; efforts to débride the wart at home decrease the need for débridement at the surgery using a scalpel where bleeding can interfere with the treatment. Next, the patient should soak the area around the wart in warm water for several minutes and then pat the area dry. An applicator is used to apply the salicylic acid product to the wart, avoiding surrounding normal skin. The area may be covered with occlusive tape, especially in high-pressure areas such as the plantar surface of the foot or to prevent clothing from rubbing off the salicylic acid. The patient should repeat this process every night until the wart clears or for 6 weeks; 2- to 3-day 'holidays' from acid application may be taken if tenderness becomes a problem. This treatment protocol (Table 5.2) can be extended for weeks or months as needed for persistent warts, so long as progress is reported.[24] The treatment protocol is similar for other formulations of salicylic acid. When using salicylic acid patches, the patches should be trimmed to fit

Table 5.1 Acid treatment methodology

Type of acid	*Strength (%)*		*No. of treatments/week*
	OTC	*Office*	
Salicyclic acid	< 17	< 70	7 (OTC)1 (Office)
MCAA, DCAA, TCAA	NA	50–95	1

DCAA, dichloroacetic acid; MCAA, monochloroacetic acid; OTC, over the counter; TCAA, trichloroacetic acid.

Table 5.2 Patient education sheet

What is salicylic acid?

Salicylic acid in various preparations is commonly used in various formulations to treat a variety of skin disorders ranging from acne to dandruff to warts. Warts are caused when a virus infects cells in the skin. Salicylic acid helps to remove warts by destroying these virus-infected cells and allowing new healthy skin cells to replace them.

Remember that warts are not easy to treat. It often takes many daily treatments over weeks or even months to get rid of warts, and there is no guarantee that this method of treatment will work for you.

How to use your salicylic acid treatment

1. Any film from previous treatments must be peeled off
2. Excess dead skin over or surrounding the wart should be scraped away. This may be done by using sandpaper, an emery board or a nail file
3. Next, soak the area around the wart in warm water for several minutes, then pat the area dry
4. Using an applicator, carefully apply the salicylic acid product to the wart, avoiding all surrounding normal skin
5. You may cover the wart with occlusive tape, especially in high-pressure areas such as the ball of the foot or to prevent rubbing by clothing
6. Repeat this process every night until the wart clears or for 6 weeks. You may take 2- to 3-day 'holidays' from treatment if the discomfort is too great
7. Call your physician if the warts have not cleared in 6 weeks, if you have any problems with excessive pain or if you notice any signs that the wart is coming back

the area of the wart, left in place overnight and changed each day.[14] There is an alternative treatment for multiple flat warts, as described by Rees[3] who recommends 1% tannic acid and 2% salicylic acid in 40% alcohol or bay rum, rubbed into the wart areas twice a day.

There are more variations in the usage of MCAA, DCAA and TCAA. As with the use of salicylic acid, excess keratotic tissue should be trimmed before applying the acid solution. Strengths varying from 50% to 95% can be applied to the wart,[18,19] and must be done with an applicator once a week by the physician, who must be careful to avoid the surrounding healthy tissue. After application of this product, the wart and surrounding skin turn white. The application may be repeated weekly until resolution is seen, or for 4 weeks, or as long as continued improvement is noted.[8,19] Treatment at the surgery using these products is favored over podophyllin in pregnant patients.

ADVERSE EFFECTS (Table 5.3)

As these acids are used topically for treating warts, there are relatively few side effects. The most commonly reported side effects for salicylic acid are tenderness and local irritation of the treatment area, which usually resolve rapidly after treatment is discontinued.[8,14] A rare case of pyogenic granuloma after combined salicylic acid treatment and cryotherapy has been reported in the literature.[25] When flat warts on the face are treated with salicylic acid, there is a lower threshold for skipping treatment when inflammation is considerable to prevent post-inflammatory hyper- and hypopigmentation in this area. An extremely rare event in the case of topical administration to large numbers of warts over a broad surface area would be salicylic acid poisoning, which manifests itself by signs and symptoms of confusion, dizziness, headache, tachypnoea and tinnitus. Although package inserts warn

Table 5.3 Adverse effects of acids

Acid	*Local effects*	*Systemic effects*
Salycylic acid	Tenderness Local irritation Pyogenic granuloma (rare) Hypopigmentation and hyperpigmentation	Salicylic acid poisoning (extremely rare from topical use): confusion, dizziness, headache, tachypnoea, tinnitus
MCAA, BCAA, TCAA	Local discomfort Superficial ulceration Scab formation Excessive pain and soreness	

against use of salicylic acid in patients with diabetes, it is possible to use this modality under a physician's supervision, recognizing that there is an increased risk of infection and slower healing in these patients. Other patients with delayed wound healing or peripheral vascular disease should also visit the physician regularly to monitor therapy.

Similarly, most adverse effects reported with the use of MCAA, DCAA and TCAA are related to local effects of the acid, with the most commonly reported being local discomfort, superficial ulceration, scab formation, and excessive pain and soreness at the area of treatment.[7,9,17,18]

COST–BENEFIT CONSIDERATIONS

There are several advantages to the use of salicylic acid. As it is available over the counter, the patient does not require a prescription or even an appointment with a healthcare professional. The treatment is inexpensive; one formulation, Duofilm, costs about 33 cents per treatment.[22] It is also easily used and controlled by the patient and is relatively free of significant side effects. Disadvantages of salicylic acid include its demand for daily involvement leading to the potential for poor compliance by the patient.[10,24]

Use of the other acids results in greater expense because usually the physician needs to apply this acid, e.g. TCAA is more expensive than most other options; the cost of achieving 100% clearance of simple condylomata is $US684, whereas extensive condylomata cost $US1288 with a mean of $US986.[19] Although these acids have side effects related mostly to local irritative effects, their expense, the need for administration by a physician and the availability of other well-reported options for physician-applied therapy have limited their use.

CASE REPORTS

Case 1

A 17-year-old high school football player presented with a 6-week history of a wart on the right ball of the foot. It had been sore when he ran, prompting his visit. The patient was having football practice every day and

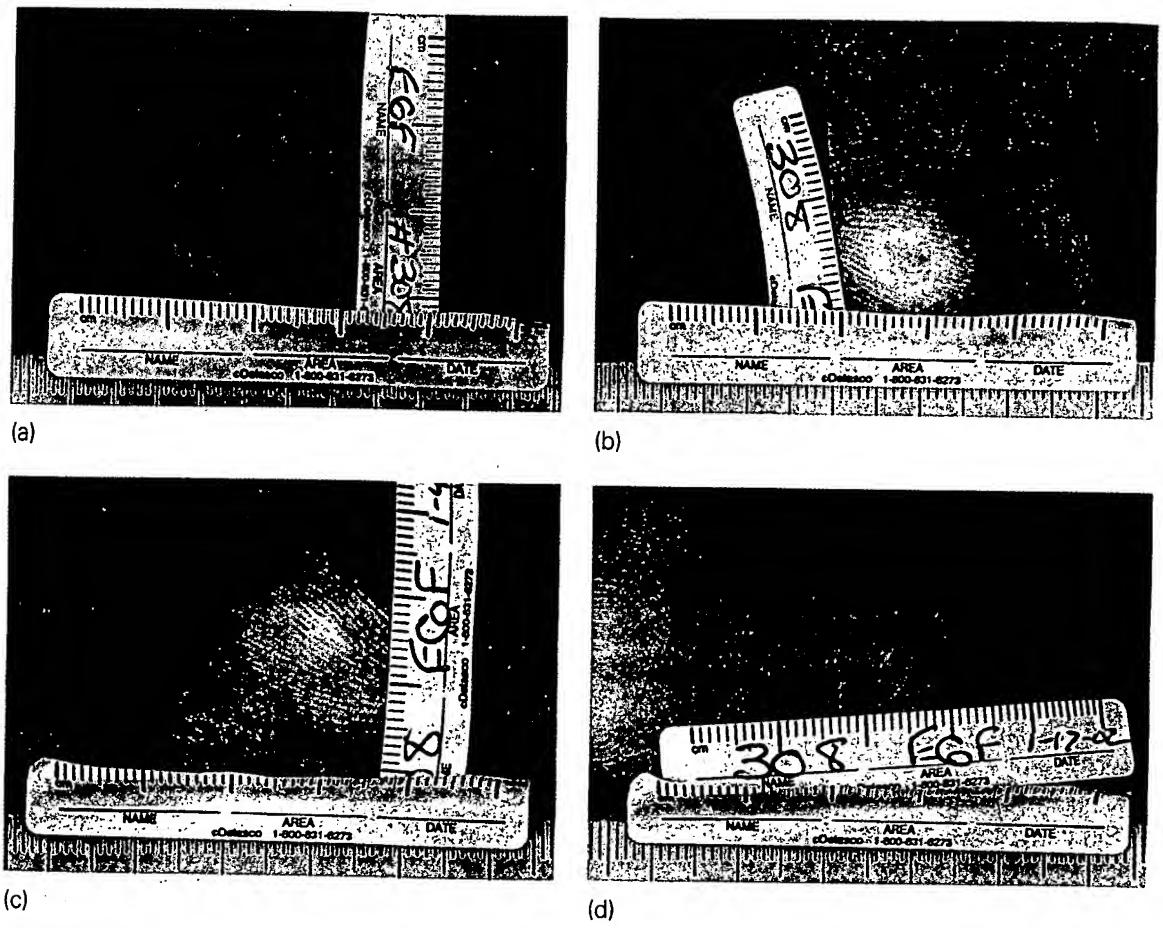
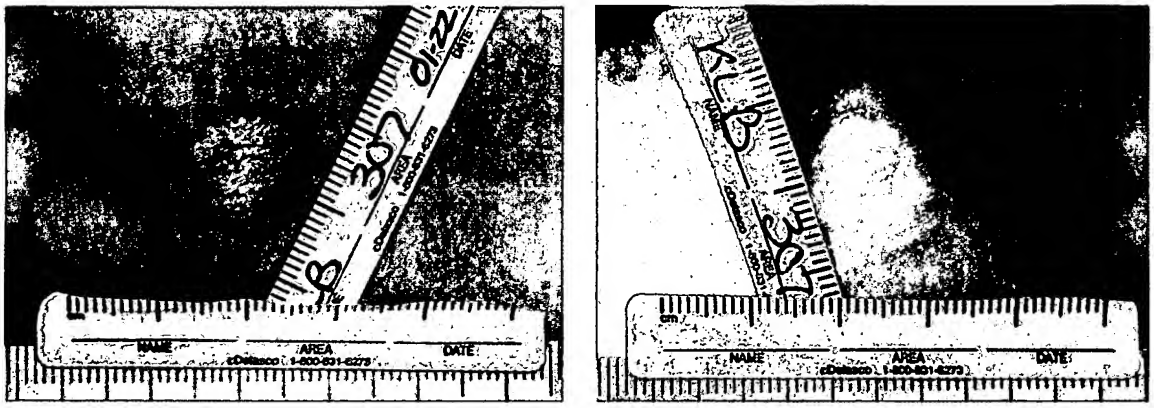


Figure 5.1
(a) A 7 × 8 mm diameter verrucous lesion with a few thrombosed capillaries is noted. Callusing is present on the surrounding skin. (b) The area of the wart now appears white after treatment with salicylic acid for 3 weeks. Thrombosed capillaries are still apparent. (c) At 8 weeks, the wart appears to be clear with some white discoloration of the skin remaining. The dermatoglyphs can be seen to move through the area where the wart was present in the past. (d) No evidence of the wart is present 2 months after discontinuation of therapy.

wanted to have a treatment that he could do at home which would not cause any pain or limit him from practising or playing football. Physical examination revealed a 7 × 8 mm diameter verrucous lesion with thrombosed capillaries and some slight callusing of the surrounding skin (Figure 5.1a). The patient was treated with 17% salicylic acid in a polyacrylic vehicle base once a day to the wart, filing it down each evening. After 3 weeks, the wart and surrounding skin had a white appearance and the wart was somewhat flatter (Figure 5.1b). The patient continued his treatment and 8 weeks after initiating therapy the wart



(a) (b)

Figure 5.2
(a) A 1.4 × 1.2 cm diameter verrucous lesion with callusing is present on the right foot at the base of the fifth toe over the metatarsal head. (b) White discoloration typical of salicylic acid-treated warts, although the wart remains despite this treatment.

appeared to be gone (Figure 5.1c). Two months later, the patient visited the doctor for another problem and the wart was entirely clear (Figure 5.1d).

Case 2

A 18-year-old woman presented for evaluation of a wart on the right lateral foot at the base of the fifth toe over the metatarsal head. The patient was away at college and wanted to have a treatment that she could use while away and would not need physician follow-up. Physical examination revealed a 1.4 × 1.2 cm diameter verrucous lesion with slight brown coloration (Figure 5.2a). The patient treated the wart every day with salicylic acid in a polyacrylic vehicle base. She filed it each evening. Four weeks later she had noted very little improvement, and 8 weeks later the area was white from denaturation of the proteins in the area with the salicylic acid although the wart persisted (Figure 5.2b). At this point the patient was home from college and the area was treated with liquid nitrogen cryotherapy every 2 weeks for three sessions; at that point the wart had cleared.

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Text Book

Viral Warts

BIOLOGY AND TREATMENT

Second edition

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Oxford New York Tokyo
OXFORD UNIVERSITY PRESS
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11

Home treatment of warts

Topical applications fall into two groups, those suitable for the home treatment of warts and those that require expert usage. There are many proprietary preparations suitable for use at home that can be bought direct from the chemists' shelves (Table 11.1, p. 96). Some of these are prescribable and are listed in the Monthly Index of Medical Specialities (MIMS). Dispensing of basic formulae is no longer economic but is sometimes necessary and Table 11.2 gives examples of some such prescriptions. A few active ingredients only are contained in these preparations, namely, salicylic acid, formalin, or glutaraldehyde. Podophyllin is now used only rarely for the treatment of skin warts.

SALICYLIC ACID PREPARATIONS

Salicylic acid is the most commonly used ingredient and is dispensed in paints, gels, pastes, or plasters.

Mode of action

Salicylic acid does not affect the virus directly but, by destroying intercellular cohesiveness in the upper part of the stratum corneum, facilitates the removal of squames containing the active virus (Huber and Christophers 1977). Increased dermal vascularity assists in the development of an immune response, which was recognized by Morison in 1975. These changes increase with an increasing concentration of salicylic acid but, as they also occur in normal skin, the application must be confined to the wart alone. There is no evidence that admixture with other substances improves the effectiveness of salicylic acid, although there is some evidence that, *in vitro* at least, permeation increases as acidity increases (Samuelov *et al.* 1979).

Choice of preparation

The choice of preparation is influenced by known effectiveness, the site and nature of the warts, the ease with which the preparation can be applied and confined to the wart, its adhesion, its side-effects, and patient acceptability.

Table 11.1 Some proprietary preparations for treating cutaneous warts available in the United Kingdom. All except those marked with an asterisk are prescribable, but in some the over-the-counter cost may be less than the prescription charge.

Name	Type	Active ingredients		Notes
		Salicylic acid	Other	
*Carnation	Ointment	10% w/w	–	Kit form
*Compound W	Paint	17%	–	
Cuplex	Gel	11%	Lactic acid 4% Copper acetate 1.1 mg %	
Duofilm	Paint	16.7%	Lactic acid 16.7%	
*Freezone	Paint	14.0%	–	
Glutarol	Paint	–	Glutaraldehyde 10% w/v	Stains brown
Posalfilin	Ointment	25%	Podophyllin 20%	
Salactol	Paint	16.7%	Lactic acid 16.7%	
Salactac	Gel	12.0%	Lactic acid 4%	No colophony
*Scholls' corn and callus solution	Solution	39.0%	–	
Taylor's corn plasters	Plaster	20%:40%	–	Packs
Veracur	Gel	–	Formaldehyde 75% w/w	
*Verucasep	Gel	–	Glutaraldehyde 10%	Stains brown
Verrugon	Ointment	50%	–	Kit form
*Wartex	Ointment	50%	–	Kit form
Novaruca	Gel	–	Glutaraldehyde 10%	Stains brown

Table 11.2 Basic formulatic
cutaneous warts. The quanti

Preparation
Formalin cream
Formalin lotion
Podophyllin compound pair
Salicylic acid collodion BPC
Salicylic and lactic acid war

Effectiveness

The effective concentrations o
cent. A collodion-based paint
equal part of lactic acid succe
common warts and 80 per cen
common with other treatment
did cure 50 per cent of them (I
acid are too strong for use o
regions. A 1 per cent salicylic
on the face helps to remove s
Hyperkeratotic warts often re
acid.

Ease of application and acc

Ease of application and acc
paints and gels, which can be
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indicate that treatment has ta
that a retaining strapping is n

Table 11.2 Basic formulations of applications for the treatment of cutaneous warts. The quantity to prescribe is shown in brackets.

Preparation	Formula
Formalin cream	Formalin solution 20%. Unquentum Merck ad 100% (10 grammes)
Formalin lotion	Formalin solution 3 mls. Water ad 100 mls. (100 mls freshly prepared)
Podophyllin compound paint BPC	Podophyllin resin 15%. Compound benzoin tincture ad 100% (5 mls)
Salicylic acid collodion BPC	Salicylic acid 12% w/v. Flexible collodion ad 100% (10 mls)
Salicylic and lactic acid wart paint	Salicylic acid 1 part, lactic acid 1 part, flexible collodion 4 parts (10 mls)

Effectiveness

The effective concentrations of salicylic acid used range from 10 to 16 per cent. A collodion-based paint containing 16 per cent salicylic acid with an equal part of lactic acid succeeded in curing, within 12 weeks, 70 per cent of common warts and 80 per cent of deep plantar warts when applied nightly. In common with other treatments, it was less successful with mosaic warts but did cure 50 per cent of them (Bunney *et al.* 1976). These strengths of salicylic acid are too strong for use on the face, in the flexures, or the anogenital regions. A 1 per cent salicylic acid cream rubbed sparingly into plane warts on the face helps to remove surface keratin if discolouration is a problem. Hyperkeratotic warts often require treatment with up to 40 per cent salicylic acid.

Ease of application and acceptability

Ease of application and acceptability are greatest for the collodion-based paints and gels, which can be applied quickly and accurately to the warts. If the applicator provided delivers too large a drop, a cocktail stick or a sharpened matchstick can be used. These applications dry quickly to form a film from which the salicylic acid is absorbed. This is usually transparent, but a few dry as a white enamel, which although not always acceptable does indicate that treatment has taken place. Adhesiveness is usually adequate so that a retaining strapping is not required except on the feet.

Higher strengths of salicylic acid are best applied as plasters, and 20 per cent and 40 per cent 'corn plasters' are commercially available. These can be cut accurately to the shape of the wart. Their adhesiveness is generally poor, however, and so it is usually necessary to hold them in place with strapping. The affected part should not be immersed in water as this allows the strong acid to seep out and damage the surrounding skin.

A novel transdermal delivery system, 15 per cent salicylic acid incorporated into small gum discs that are held in place overnight with transparent tape, is reported to be effective, easy to use, and acceptable, and will shortly be available in the United Kingdom.

Side-effects

Hypersensitivity reactions are rare and are not usually due to salicylic acid itself but to colophony, which is an ingredient of most of the collodion bases used, although it has been omitted from the recently produced product Salactac. As colophony is also found in some plaster adhesives, reaction to these might serve as a warning. Most of the discomfort experienced with salicylic acid preparations is due to its excessive or injudicious application (Fig. 11.1).

Fig. 11.1 Maceration of the skin surrounding warts after application of excessive salicylic acid paint and plaster.

PREPARATIONS

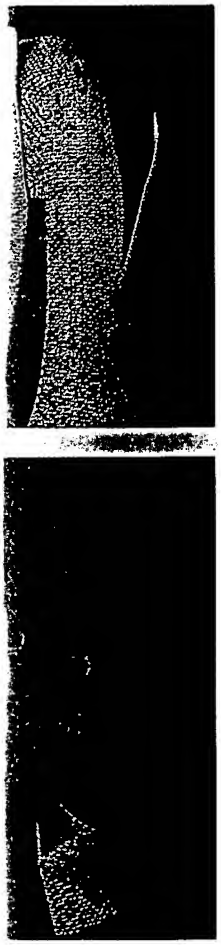
Formalin is a 40 per cent solu
dilutions of formalin are well
Vickers (1961) and Anderso
80 per cent and 62 per cent
sidered by some, including L
mosaic warts. Anderson and
the mosaic warts in their trial.
into the category of home trea
on the weight bearing areas o
thick, as it will cause cracking

Mode of action

Formalin is well known for it
skin it causes anhidrosis and d
reactions. It is a powerful disi
exposure to 0.4 per cent for
When formalin is applied to w
ably occurs in addition to the
skin. Lewis (1973) reported a
warts disappeared when cha
possible that a local allerg
mechanism of cure.

Choice of preparation and

This is more complicated t
Contamination of the skin su
lation of a suitable prepar
collodion and so adhesive p
to incorporate formalin into
successful base is Unguentu
aids penetration of the medi
to 20 per cent of formalin
(Table 11.2, p. 97). This pre
accurately into the area of w
absorbed and so does not
plaster, as is the case with m
after preliminary preparatio
0.75 per cent w/w formald
available (Table 11.1, p. 96)



refoot to prevent it rolling back
vertically and (b) the strips of
ured on top. Encircling plasters

adding to the region of plantar
ent behind the affected area is
ads.

(d) Cautions

1. Home treatment of facial warts is best avoided.
2. Nearly all preparations will damage polished wood.
3. All preparations should be kept out of the reach of small children.

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This report reflects the best data available at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

Guidelines of care for warts: Human papillomavirus

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I. Introduction

The American Academy of Dermatology's Committee on Guidelines of Care is developing guidelines of care for our profession. The development of guidelines will promote the continued delivery of quality care and assist those outside our profession in understanding the complexities and scope of care provided by dermatologists. For the benefit of members of the American Academy of Dermatology who practice in countries outside the jurisdiction of the United States, the listed treatments may include agents that are not currently approved by the U.S. Food and Drug Administration.

II. Definition

Warts are benign tumors that commonly involve the skin and other epithelial tissues. The etiologic agents for these infections are a class of double-stranded DNA viruses called papillomaviruses. Warts are generally classified by their clinical features and morphology (e.g., common, flat, filiform) or by location (e.g., genital, plantar, respiratory papillomatosis).

III. Rationale

A. Scope

Human papillomaviruses (HPV) infect individuals of all ages. Clinical lesions are most common in children and young adults, with an estimated incidence of 10%. Although the prevalence of HPV in the adult population is not known, various diagnostic techniques, including serology and DNA hybridization, suggest that exposure to the virus and subclinical and latent infection may be very common. Infection occurs as a result of person-to-person spread, including that of sexual transmission, vertical transmission, and from exposure to virus in the environment. In fact, HPV infection is now the most common sexually transmitted disease. In the past 20 years, according to fig-

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J AM ACAD DERMATOL 1995;32:98-103.

0190-9622/95 $3.00 + 0 16/1/58668

3. Treatment modalities may vary according to a number of factors:
   a) Age of patient
   b) Duration of warts
   c) Location of warts
   d) Extent of warts
   e) Type of warts (mosaic, flat warts)
   f) Patient's immune status
   g) Other disorders patient may have: Diabetes, cold intolerance
   h) Pain tolerance
   i) Inconvenience of some treatments requiring multiple trips
   j) Risk of scarring
   k) Experience of the physician with certain modalities (e.g., laser)
   l) Other
4. Medical treatment
   The listed treatments may be used singly, in combination with each other, or with a surgical modality.
   a) Common
      1) Caustics/acids: Salicylic acid, iactic acid, monochloroacetic acid, bichloroacetic acid, trichloroacetic acid, nitric acid, and others
      2) Cantharidin
      3) Podophyllin resin: Especially in anogenital HPV. A purified form of this resin containing podofilox as 0.5% solution is available.
      4) Tretinoin
      5) Bleomycin: Intralesional
      6) 5-Fluorouracil: Topical
      7) Other
   b) Less common
      1) Oral etretinate or vitamin A
      2) X-ray: Not in laryngeal papillomatosis or epidermodysplasia verruciformis
      3) Heat and tape occlusion
      4) Other
   c) Evolving treatments
      1) Interferon alfa: Intralesional or intramuscular
      2) Other
   d) Inappropriate treatments
      At the present time no type of wart vaccine is recommended. Because the placebo response is high, unsupported systemic treatments should be questioned.
5. Surgical treatment
   The listed treatments may be used singly, in combination with each other, or in combination with other nonsurgical modalities.
   a) Common
      (1) Cryosurgery
      (2) Carbon dioxide slush (dry ice and acetone)
      (3) Electrosurgery & curettage
      (4) Blunt dissection
      (5) Carbon dioxide laser may be used for the treatment of extensive, recurrent, or recalcitrant warts. It may be used in conjunction with other modalities including electrosurgical debulking, interferon, and/or postoperative 5-fluorouracil.
   b) Less common
      (1) Excision
      (2) Other
6. Other treatments
   a) No treatment (spontaneous resolution) to allow development of immunity to the virus
   b) Hypnosis and other forms of suggestion
7. Evolving treatments
   a) Photodynamic therapy
   b) Pulsed dye, Q-switched, and copper vapor lasers, which are directed at the vascular component of the wart, may be useful.
   c) Induction of delayed-type hypersensitivity (e.g., squaric acid dibutylester, topical *Rhus*, intralesional tuberculin, dinitrochlorobenzene)
   d) Colchicine, cimetidine
   e) Other

B. Patient education
   Patients should be aware of the following:
   1. The wart virus persists after therapy and some degree of infectivity may remain even in the absence of clinical lesions. Patients with a history of anogenital warts need appropriate clinical follow-up because of the potential oncogenicity of some HPV types.
   2. Some warts can regress spontaneously; therefore no treatment may be an option.
   3. The behavior of individual lesions is not totally predictable and lesions may not respond optimally to treatment.
   4. The presence of local as well as systemic immunity may be necessary to eradicate the clinical manifestations of HPV.

C. Miscellaneous
   The use of many of these nonsurgical approaches may be contraindicated during pregnancy or in females likely to become pregnant during the treatment period, or in children.
   Treatment intervals may vary considerably